CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	217836
Supporting document/s:	SDN001
Applicant's letter date:	12/22/2022
CDER stamp date:	12/22/2022
Product:	Qlosi® (Pilocarpine hydrochloride ophthalmic solution, 0.4%)
Indication:	For the treatment of presbyopia in adults
Applicant:	Orasis Pharmaceuticals Ltd c/o Premier Consulting LLC (Newark, CA)
Review Division:	DPT- ORPURM/OSM, supporting the Division of Ophthalmology Products (DO)
Reviewer:	Erin Ruhland, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Mukesh Summan, PhD, DABT
Project Manager:	Diana Willard

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1 Executive Summary

1.1 Introduction

The Applicant has filed a 505(b)(1) NDA for Qlosi® (pilocarpine hydrochloride ophthalmic solution, 0.4%) for the treatment of presbyopia in adults. All nonclinical elements of the NDA were either 1) referenced from NDA 020237 (Salagen) with the Applicant obtaining right of reference from the NDA holder for those studies, or 2) provided through the conduct of GLP studies. The NDA is approvable from a Nonclinical Pharmacology/Toxicology perspective.

1.2 Brief Discussion of Nonclinical Findings

- For nonclinical systemic safety, pharmacology and drug metabolism, the Applicant has obtained right of reference for NDA 020237 (Salagen).

- Salagen labeling has not undergone PLLR conversion, however most information required by guidance for the PLLR formatted label for this application are present in the Salagen labeling.

- The Applicant provided a nonclinical chronic ocular toxicity study to support ocular safety of the formulation and a 28-day ocular toxicity study to support qualification of impurities.

- No adverse toxicity was associated with the Applicant's formulation or the qualified impurities. These studies are adequate for approval.

1.3 Recommendations

- **1.3.1 Approvability**

    - **NDA 217836 is approvable at the proposed dose indicated from the nonclinical pharmacology/toxicology discipline standpoint.**

- **1.3.3 Labeling**

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

2 Drug Information

2.1 Drug

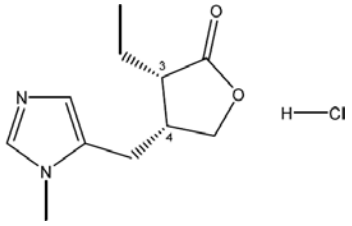
CAS Registry Number: 54-71-7

Generic Name: Pilocarpine hydrochloride

Chemical Name: 3-Ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)-methyl]-2(3*H*)-furanone hydrochloride *or* 2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1*H*imidazol-5-yl)-methyl]-monohydrochloride, (3*S*-*cis*)

Molecular Formula/Molecular Weight: $C_{11}H_{16}N_2O_2 \cdot HCl$ / 244.72 g/mol

Structure:



Pharmacologic Class: Cholinergic agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 131464: CSF-1 (pilocarpine hydrochloride ophthalmic solution, 0.4%)
- NDA 020237 (right of reference obtained by Applicant): Salagen, tablet; oral
  - Approved 3-22-1994
  - A Pharmacology/Toxicology review of the initial NDA application was not found online.
  - Indicated for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; and the treatment of symptoms of dry mouth in patients with Sjogren's Syndrome.
  - Approved dose range 15-30 mg per day (not to exceed 10 mg per dose).
- DMF (b) (4)

2.3 Drug Formulation

Component	Concentration		Quantity per unit[1] (mg)	Function	Quality Standard
	mg/mL	% w/v			
Pilocarpine hydrochloride	4.0	0.4	1.6	Drug substance	USP
Hypromellose (b) (4)	(b) (4)				USP-NF
Sodium chloride					USP-NF
Sodium hyaluronate					Ph. Eur.
Disodium edetate[2]					USP-NF
Sodium hydroxide[3]	q.s. to target pH	q.s. to target pH	q.s. to target pH	pH adjuster	USP-NF
Hydrochloric acid[3]					USP-NF
Water for Injection (WFI)	(b) (4)				USP-NF

USP: United States Pharmacopeia; mg: milligram; mL: milliliter; NF: National Formulary; Ph. Eur.: European Pharmacopeia; q.s: *quantum satis;* w/v: weight/volume

1 Unit: is 0.4 mL ophthalmic solution per vial

2 As dihydrate

3 Used as (b) (4) solution

2.4 Comments on Novel Excipients

- Hypromellose (b) (4)
  - Hypromellose is qualified to a concentration of 0.5% for topical ophthalmic solutions and suspensions (per inactive ingredient database)
  - The Applicant's formulations contain (b) (4)% Hypromellose (b) (4)
  - No toxicity was associated with the vehicle in a chronic ocular toxicity study in rabbits.
  - The excipient is considered qualified in the Applicant's formulation at a concentration of (b) (4)%.
- Sodium hyaluronate
  - Sodium hyaluronate is not qualified for topical ophthalmic instillation (per inactive ingredient database search for "hyaluronate sodium". "Hyaluronate sodium" is qualified for intravitreal use at concentrations up to 2.3%.
  - The Applicant's formulations contain (b) (4)% sodium hyaluronate.
  - No toxicity was associated with the vehicle in a chronic ocular toxicity study in rabbits.
  - The excipient is considered qualified in the Applicant's formulation at a concentration of (b) (4)%.

2.5 Comments on Impurities/Degradants of Concern

- [redacted]
  - The Applicant proposes a specification of [redacted] (% labeled strength of API; a daily dose of [redacted] mg/eye/day at MRHOD).
  - The Applicant qualified [redacted] up to [redacted]% (drug product administered TID) or [redacted] mg/eye/day in the 28-day ocular toxicity study reviewed below.
  - The Applicant's specification is qualified from a toxicologic perspective.

- [redacted]
  - The Applicant proposes a specification of [redacted] (a daily dose of [redacted] mg/eye/day at MRHOD).
  - The Applicant qualified [redacted] up to [redacted]% (of drug product administered TID) or [redacted] mg/eye/day in the 28-day ocular toxicity study reviewed below.
  - The Applicant's specification is qualified from a toxicologic perspective.

[redacted]

2.6 Proposed Clinical Population and Dosing Regimen

- Qlosi® is indicated for the treatment of presbyopia in adults.
- The recommended dosage of Qlosi® is one drop in each eye. This can be repeated a second time after 2-3 hours for an effect up to 8 hours. Qlosi can be administered on a daily basis, or as needed, up to twice each day.
- With a drop volume of [redacted] mL/drop and the maximum daily dose of 2 drops/eye, the total daily ocular dose is [redacted] mg/eye/day or [redacted] mg/day total daily dose when administered bilaterally.

3 Studies Submitted

3.1 Studies Reviewed

- Study ORP-21-01: *In vitro* effect of pilocarpine on hERG current (iKr) expressed in human embryonic kidney (HEK) cells
- Study 21-130-0026: Pharmacokinetic study following a single topical ocular dose administration of CSF-1 in New Zealand White rabbits
- Study 21-1291: 6-month topical ocular toxicity and toxicokinetic study of CSF-1 (pilocarpine HCl 0.4% w/v ophthalmic solution) in Dutch-Belted rabbits (with a 4-week recovery)
- Study 21-1296: 28-day topical ocular toxicity study of CSF-1 (pilocarpine HCl 0.4% w/v ophthalmic solution) containing elevated levels of (b) (4) and (b) (4) impurities in Dutch-Belted rabbits

3.2 Studies Not Reviewed

- Study ORP-21-01-AC: Analytical validation of assay and stability study of pilocarpine in DI water and HB-PS formulations
- Study 3887-2101: Validation of a method for the determination of pilocarpine in rabbit plasma by LC-MS/MS
- Study 3887N-2104: Qualification of a method for the determination of pilocarpine in rabbit eye tissue homogenate by LC-MS/MS

4 Pharmacology

4.1 Primary Pharmacology

- Pilocarpine hydrochloride is a cholinergic muscarinic agonist that activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Pilocarpine contracts the iris sphincter muscle, constricting the pupil to enhance the depth of focus and improve near and intermediate visual acuity while maintaining some pupillary response to light.
- Pilocarpine contracts the ciliary muscle, facilitating accommodation.

4.2 Safety Pharmacology

Study ORP-21-01: In vitro effect of pilocarpine on hERG current (iKr) expressed in human embryonic kidney (HEK) cells

- This study determined the potential for pilocarpine to inhibit hERG ion channels at physiologic temperatures using stably transfected human embryonic kidney (HEK 293) cell lines. Currents were measured using the whole-cell variant of the patch clamp method (Crumb *et al*., 2016).
- Pilocarpine HCl (Batch# VC-2003) was tested over a concentration range of 0.1 – 30 µM.

- Pilocarpine had no effect on hERG current amplitude with the concentration of 30 μM being associated with a 3.4 ± 0.7% reduction as compared to the vehicle/time control which was associated with a 2.5 ± 2.6% reduction. The response to the positive control, dofetilide, with an IC_{50} of 0.94 nM, and to the vehicle control demonstrated proper system performance.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study 21-130-0026: Pharmacokinetic study following a single topical ocular dose administration of CSF-1 in New Zealand White rabbits

- This study determined ocular and systemic pharmacokinetics of pilocarpine in New Zealand White rabbits following bilateral topical ocular instillation of the clinical formulation (CSF-1; drop volume (b) (4) mL/drop; total dose (b) (4) mg pilocarpine/eye)
- At 0.083, 0.25, 0.5, 1, 3, and 6 hr after dose administration, 3 animals per time point were bled for plasma samples, euthanized, the eyes enucleated and then dissected. Ocular tissues evaluated for pilocarpine concentration were conjunctival, cornea, aqueous humor, iris/ciliary body, lens, vitreous, retina, choroid/RPE, sclera, and optic nerve head. Plasma samples (3/time point) and ocular tissues (6/time point) were analyzed for pilocarpine levels using a qualified LC-MS/MS method.
- Results
    - T_{max} for anterior ocular tissues tended to occur at the first time point (0.083 hr), whereas more posterior ocular tissues (ICB, lens, vitreous, OHN) exhibited a later T_{max}.
    - Highest exposures occurred in the aqueous humor, sclera and choroid/RPE, and then the ICB (drug target) and retina, with the lowest exposures in the lens and vitreous.

Pharmacokinetic parameters of pilocarpine in rabbit plasma and ocular tissues after a single, bilateral administration of CSF-1 in rabbits

Dose Level (mg/eye)	Matrix	LOQ (ng/g or ng/mL)	C_{max} (ng/g or ng/mL)	T_{max} (hr)	AUC_{0-t} (hr*ng/g or hr*ng/mL)	$T_{1/2}$ (hr)
(b) (4)	Cornea	5.0	10400	0.083	3750	1.09
	Conjunctiva	5.0	5810	0.083	6410	NC
	Aqueous Humor	2.5	2700	0.083	1680	NC
	ICB	5.0	517	0.25	406	0.548
	Lens	5.0	131	0.5	293	NC
	Vitreous	2.5	71.3	0.5	94.7	NC
	Retina	5.0	408	0.083	508	1.53
	Choroid/RPE	5.0	448	0.083	1170	NC
	Sclera	5.0	1460	0.083	1940	NC
	ONH	5.0	561	1.0	794	NC
	Plasma	0.5	29.2	0.083	8.01	0.206

Abbreviations: AUC – area under the curve; Cmax – maximal concentration; ICB – iris/ciliary body; NC – could not be calculated; ONH – optic nerve head; RPE – retinal pigmented epithelium; T1/2 – half-life; Tmax – time of Cmax.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 6-month topical ocular toxicity and toxicokinetic study of CSF-1 (pilocarpine HCl 0.4% w/v ophthalmic solution) in Dutch-Belted rabbits (with a 4-week recovery)

Study no.: 21-1291
Study report location: \\CDSESUB1\EVSPROD\nda217836\0001\m4\42-stud-rep\423-tox\4236-loc-tol\21-1291\21-1291-audited-draft-rpt.pdf
Conducting laboratory and location: (b) (4)
Date of study initiation: 9/27/2021
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Pilocarpine hydrochloride 0.4% (CSF-1); Lot#s 4N99 and 5N01; purity 99% and 98.6%, respectively.

Key Study Findings

- Administration of the high-dose (0.4% CSF-1 (b) (4) drops per time interval, (b) (4) mg/eye/day) was well tolerated and no test article-related findings were noted in ophthalmic examinations, IOP, or corneal thickness during the study.
- Systemically, there were no vehicle- or test article-related findings in clinical observations, body weight, clinical pathology, gross necropsy findings, organ weights, or histopathological evaluations of the eyes, ocular adnexa, and systemic tissues.
- Based on the results of this study, the no observed adverse effect level (NOAEL) was considered to be (b) (4) mg/eye/day ((b) (4) mg/day total bilateral dose).

Methods

Doses:

Study Group	Group Name	Dose Amount/ Eye[a]	Pilocarpine HCL Conc. (%)	Total Dose Volume (µL/ day)[b]	Total Dose of Pilocarpine/ Eye (total dose/ animal)	Number of Rabbits/Group	
						Core	Recovery
1	Vehicle Control	(b) (4) drops	0.0	(b) (4)	0 mg (0 mg)	5/sex	3/sex
2	Low Dose	drops	0.4		(b) (4) mg mg)	5/sex	3/sex
3	High Dose	drops	0.4		(b) (4) mg mg)	5/sex	3/sex

(b) (4)

(b) (4)

(b) (4)

Group 2: Bilateral; 0.4% BID (b) (4) given as (b) (4) (b) (4)

Group 3: Bilateral; 0.4% TID ((b) (4) drops/eye/day); dosed at same interval as Group 1 (vehicle); Total daily dose: (b) (4) mg/eye/day

Route of administration: Topical ocular instillation
Dose volume: 0.(b) (4) mL/drop
Formulation/Vehicle:
Species/Strain: Rabbit / Dutch-Belted
Number/Sex/Group: Core: 5/sex/group
Recovery: 3/sex/group
Age: 4 – 5 months
Weight: 1.5 – 2.1 kg
Deviation from study protocol: No deviations affected the conduct or interpretability of study results.

Observations and Results

Mortality

- No animals died or were sacrificed prior to schedule

Clinical Signs (cageside: daily; detailed: twice daily during first week of dosing and weekly thereafter)

- No changes in clinical signs attributed to the test article.

Body Weights (weekly)

- No changes in body weight attributed to the test article.

Feed Consumption (daily; qualitative)

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (twice daily during first week of dosing and weekly thereafter; slit lamp / indirect ophthalmoscopy; Hackett-McDonald and Draize scoring)

Tonometry (pre-test, monthly, and at recovery)

- No changes in intraocular pressure attributed to the test article.

Pachymetry (pre-test, monthly, and at recovery)

- No changes in corneal thickness attributed to the test article.

Hematology (pre-test and prior to scheduled sacrifice)

- No changes in hematological parameters attributed to the test article.

Clinical Chemistry (pre-test and prior to scheduled sacrifice)

- No changes in clinical chemistry parameters attributed to the test article.

Gross Pathology

- No changes in macroscopic observations attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Full standard battery

Peer Review: No

Histological Findings: No changes in microscopic findings attributed to the test article.

Toxicokinetics APPEARS THIS WAY ON ORIGINAL

Day	Group	Pilocarpine HCl Dose (total mg/day)	Sex	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL) [a]	AUC_{last} (hr*ng/mL)[a]
1	2 (Low Dose)	2.16	M	[b]	0.25	8.13	5.90
			F	[b]	0.25	9.12	5.96
1	3 (High Dose)	3.24	M	1.1	0.5	18.3	23.0
			F	[b]	0.25	15.8	7.69
180	2 (Low Dose)	2.16	M	[b]	0.25	17.5	11.7
			F	[b]	0.5	16.8	25.4
180	3 (High Dose)	3.24	M	[b]	0.25	40.8	33.2
			F	3.6	0.25	36.5	57.0

Dosing Solution Analysis

- The dosing solution remained stable throughout the dosing period.

Study title: 28-day topical ocular toxicity study of CSF-1 (pilocarpine HCl 0.4% w/v ophthalmic solution) containing elevated levels of (b) (4) and (b) (4) impurities in Dutch-Belted rabbits

Study no.: 21-1296
Study report location: \\CDSESUB1\EVSPROD\nda217836\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42376-imp\21-1296\21-1296.pdf
Conducting laboratory and location: (b) (4)
Date of study initiation: 9/27/2021
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity:

- Pilocarpine hydrochloride (nominal); Lot# (b) (4) 99.6% pilocarpine hydrochloride / (b) (4)
- Pilocarpine hydrochloride (stressed); Lot# (b) (4) 89.6% pilocarpine hydrochloride / (b) (4) % (b) (4) / (b) (4) % (b) (4)

Key Study Findings

- Administration of the clinical vehicle, pilocarpine hydrochloride (nominal), and pilocarpine hydrochloride (stressed, i.e. containing high impurities) was well tolerated in male and female Dutch-Belted rabbits when administered via bilateral topical ocular instillation (b) (4) for 28 consecutive days.
- There were no attributable clinical observations or changes in body weight or body weight gain. No vehicle or test article-related findings were noted in ophthalmic examinations, IOP, or corneal thickness. There were no changes in clinical pathology, gross necropsy findings, organ weights, or histopathological evaluations of the ocular tissues.
- The no observed effects related to topically administered CSF-1 High Impurities, containing (b) (4)% (b) (4) ((b) (4) mg/mL (b) (4) µg/eye/day]) and (b) (4)% (b) (4) mg/mL (b) (4) µg/eye/day]), compared to CSF-1 Nominal, containing (b) (4) mg/mL [(b) (4) µg/eye/day]) and (b) (4)% (b) (4) mg/mL IPC [(b) (4) µg/eye/day]), or as compared to topically administered CSF-1 vehicle.

Methods

Doses:

Study Group	Group Name	Test Article Composition (%)[a]		Dose Conc. (mg/mL)	Total Dose[b] (µg/eye/day)	Number of Rabbits
1	CSF-1 Vehicle Control (Lot# 4N98)	API (b) (4)	0 0 0	0 0 0	0 0 0	4/sex
2	CSF-1 Nominal (Lot# 5N00)	API (purity)	0.4[c] (99.6%)	4	540[c] (b) (4)	4/sex
3	CSF-1 High Impurities (Lot# (b) (4) stressed)	API (purity) (b) (4)	0.4[c] (b) (4)	(b) (4)	(b) (4)	4/sex

(b) (4)

Frequency of dosing: TID
Route of administration: Topical ocular instillation
Dose volume: (b) (4) mL/drop
Formulation/Vehicle: Clinical formulation with or without added impurities
Species/Strain: Rabbit / Dutch-Belted
Number/Sex/Group: 4/sex/group
Age: 4 – 5 months
Weight: 1.2 – 1.7 kg
Deviation from study protocol: No deviations affected the conduct or interpretability of the study.

Observations and Results

Mortality

- No animals died or were sacrificed prior to schedule

Clinical Signs (cageside: daily; detailed: weekly)

- No changes in clinical signs attributed to the test article.

Body Weights (pre-test and then weekly)

- No changes in body weight attributed to the test article.

Feed Consumption (daily; qualitative)

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy (pre-test and prior to scheduled sacrifice; fluorescein staining / slit lamp / indirect ophthalmoscopy; Hackett-McDonald scoring)

- No changes in ophthalmoscopic observations attributed to the test article.

Tonometry (pre-test and prior to scheduled sacrifice)

- No changes in intraocular pressure attributed to the test article.

Pachymetry (pre-test and prior to scheduled sacrifice)

- No changes in corneal thickness attributed to the test article.

Hematology (pre-test and prior to scheduled sacrifice)

- No changes in hematological parameters attributed to the test article.

Clinical Chemistry (pre-test and prior to scheduled sacrifice)

- No changes in clinical chemistry parameters attributed to the test article.

Gross Pathology

- No changes in macroscopic observations attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Ocular tissues and adnexa only. For the eyes, three sagittal sections/eye with at least one section to include the visual streak and optic nerve.

Peer Review: No

Histological Findings: No changes in microscopic findings attributed to the test article.

Dosing Solution Analysis

- The dosing solution remained stable throughout the dosing period.

7 Genetic Toxicology

Salagen® labeling:

No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an in vitro chromosome aberration assay in a Chinese hamster ovary cell line; 3) an in vivo chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Applicant proposed labeling statement:

Mutagenesis
Pilocarpine did not show any potential to cause genetic toxicity in a series of studies that included: 1) bacterial assays (Salmonella and *E. coli*) for reverse gene mutations; 2) an *in vitro* chromosome aberration assay in a Chinese hamster ovary cell line; 3) an *in vivo* chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

8 Carcinogenicity

Salagen® labeling:

Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30 mg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males

and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.

Applicant proposed labeling statement:

Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage level studies (up to 30 mg/kg/day; approximately 200-fold higher than the MRHOD of 0.012 mg/kg/day, on a mg/m^2 basis). In rats, an oral dose of 18 mg/kg/day (approximately 240-fold higher than the MRHOD (b) (4) resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both male and female rats, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats.

Reviewer's note: The Applicant's calculation of the safety margins is correct.

- **Total daily human ocular dose: (b) (4) mg**

- Total daily human ocular dose: (b) (4) mg
  - For 60 kg adult = (b) (4) mg/kg
  - BSA conversion: (b) (4) mg/m^2
- Rat tumorigenic dose: 18 mg/kg
  - BSA conversion: 18 x 6 = 108 mg/m^2
  - Dose margin calculation: 108 / 0.444 = 243.2-fold
    - Rounded to 240-fold for labeling purposes.

- Mouse NOAEL dose (no increase in tumors): 30 mg/kg
  - BSA Conversion: 30 x 3 = 90 mg/m^2
  - Dose margin calculation: 90 / 0.444 = 202.7-fold
    - Rounded to 200-fold for labeling purposes.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Salagen® labeling:

Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (mg/m^2) estimates) for six months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. SALAGEN® Tablets should be administered to individuals who are attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.

Applicant Labeling Statement:

Pilocarpine oral administration to male and female rats at a dosage of 18 mg/kg/day (approximately 240-fold higher than the MRHOD of 0.012 mg/kg/day, on a mg/m^2 basis) resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphological evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on males, females, or both. In dogs, exposure to pilocarpine at (b) (4) *dosage of 3 mg/kg/day for 6 months resulted in evidence of impaired spermatogenesis (approximately 135-fold higher than the MHROD of 0.012 mg/kg/day, on a mg/m^2 basis).*

Reviewer's note: The Applicant's calculation of the safety margins is correct.

- **Total daily human ocular dose:** (b) (4) **mg**
  - For 60 kg adult = (b) (4) mg/kg
  - BSA conversion (human k_m = (b) (4) kg/m^2): (b) (4) = (b) (4) mg/m^2
- Rat toxic dose (impaired fertility): 18 mg/kg
  - BSA conversion (rat k_m = 6 kg/m^2): 18 x 6 = 108 mg/m^2
  - Dose margin calculation: 108 / 0.444 = 243.2-fold

- Rounded to 240-fold for labeling purposes.

- Dog toxic dose (sperm motility): 3 mg/kg
  - BSA conversion (dog k_m = 20 kg/m^2): 3 x 20 = 60 mg/m^2
  - Dose margin calculation: 60 / 0.444 = 135.1-fold
    - Rounded to 135-fold for labeling purposes.

9.2 Embryonic Fetal Development

Salagen® labeling:

Pregnancy: Teratogenic Effects
Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates). These effects may have been secondary to maternal toxicity.

Applicant Labeling Statement:

Risk Summary
There are no (b) (4) *Qlosi in pregnant women to inform any drug associated risks.*

Animal Data
In embryofetal development studies, oral administration of pilocarpine to pregnant rats throughout organogenesis produced maternal toxicity, skeletal anomalies and reduction in fetal body weight at 90 mg/kg/day (approximately 1200-fold higher than the maximum recommended human ophthalmic dose [MRHOD] of 0.012 mg/kg/day, on a mg/m^2 basis).

Reviewer's note: The Applicant's calculation of the safety margins is correct.

- Total daily human ocular dose: (b) (4) mg
  - For 60 kg adult = (b) (4) mg/kg
  - BSA conversion (human k_m = (b) (4) kg/m^2): (b) (4) x (b) (4) = (b) (4) mg/m^2
- Rat toxic dose (increased skeletal variations): 90 mg/kg
  - BSA conversion (rat k_m = 6 kg/m^2): 90 x 6 = 540 mg/m^2

- Dose margin calculation: 540 / 0.444 = 1216-fold
  - Rounded to 1200-fold for labeling purposes.

9.3 Prenatal and Postnatal Development

Salagen® labeling:

In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 mg/kg/day (approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) and above.

Applicant Labeling Statement:

In a peri-/postnatal study in rats, oral administration of pilocarpine during late gestation through lactation increased stillbirths at a dose of 36 mg/kg/day (approximately 475-fold higher than the MRHOD of 0.012 mg/kg/day, on a mg/m^2 basis). Decreased neonatal survival and reduced mean body weight of pups were observed at ≥18mg/kg/day (approximately 240-fold higher than the MRHOD of 0.012 mg/kg/day, on a mg/m^2 basis).

Reviewer's note: The Applicant's calculation of the safety margins is correct.

- Total daily human ocular dose: (b) (4) mg
  - For 60 kg adult = (b) (4) mg/kg
  - BSA conversion (human k_m = (b) (4) kg/m^2): (b) (4) x (b) (4) = (b) (4) mg/m^2
- Rat toxic dose (decreased survival and body weight of pups): 18 mg/kg
  - BSA conversion (rat k_m = 6 kg/m^2): 18 x 6 = 108 mg/m^2
  - Dose margin calculation: 108 / 0.444 = 243.2-fold
    - Rounded to 240-fold for labeling purposes.
- Rat toxic dose (increased stillbirths): 36 mg/kg
  - BSA conversion (rat k_m = 6 kg/m^2): 6 x 36 = 216 mg/m^2
  - Dose margin calculation: 216 / 0.444 = 486.5-fold
    - Rounded to 475-fold for labeling purposes.

9.5. Lactation

Salagen® labeling:

> *It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SALAGEN® Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.*

The Applicant proposes the following labeling statement which differs from the approved Salagen® labeling in Section 8.2:

> Risk Summary
> *There are no data on the presence of pilocarpine in human milk, the effects on breastfed infants, or the effects on milk production to inform the risk of Qlosi to an infant during lactation. Systemic levels of pilocarpine following topical ocular administration are low (see Clinical Pharmacology, 12.3), and it is not known whether measurable levels of pilocarpine would be present in maternal milk following ocular administration of Qlosi.*
>
> *The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Qlosi and any potential adverse effects on the breastfed child from Qlosi.*

*The Applicant has referenced the following publication (Omori, Y, *et al*., 2004) in the application but did not propose a labeling statement to summarize these findings. In order to maintain consistency with other approved pilocarpine formulations, the following labeling statements regarding the presence of pilocarpine in lactating rats are proposed:

Added to the Risk Summary: *Pilocarpine and/or its metabolites are excreted in the milk of lactating rats following single oral administration.*

> **Added to Animal Data under Section 8.2:** *Following a single oral administration of ^{14}C-pilocarpine to lactating rats, the radioactivity concentrations in milk were similar to those in plasma. Peak concentrations were observed at 0.5 h, with both milk and plasma levels declining at similar rates, but still detectable at 24 h.*

Omori, Y., *et al*., 2004, "Absorption, distribution and excretion of 14C-pilocarpine following oral administration to rats", *Arzneim. Forsch Drug Res*, 54: 171 – 178.

- After single oral doses to nursing rats (0.3 mg/kg), ^{14}C-labeled pilocarpine was detected in milk and plasma (see below). Similar peak concentrations were

observed in the milk and plasma at 0.5 h and concentrations declined subsequently at similar rates, both being still detectable at 24 h.

Mean plasma and milk concentrations of radioactivity after single 0.3 mg/kg oral doses of ^{14}C-pilocarpine hydrochloride to nursing rats.

Sampling time (h)	Concentration of radioactivity (ng equivalents/g)	
	Plasma	Milk
0.5	126 ± 9	123 ± 13
2	36 ± 4	39 ± 2
8	4 ± 1	8 ± 1
24	1 ± 0	1 ± 0

11 Integrated Summary and Safety Evaluation

The Applicant has filed a 505(b)(1) NDA for Qlosi® (pilocarpine hydrochloride ophthalmic solution, 0.4%) for the treatment of presbyopia in adults. All nonclinical elements of the NDA were either referenced from NDA 020237 (Salagen), or through the conduct of GLP studies. The NDA is approvable from a Nonclinical Pharmacology/Toxicology perspective.

Toxicity	Species	NOAEL (mg/eye)	Safety Margin Based on unilateral ocular dose (mg/eye)*
No adverse toxicity	Rabbit	(b) (4) mg/eye/day	4.4-fold

*Maximum recommended human ocular dose: (b) (4) mg/eye/day

12 Appendix/Attachments

Current Salagen Labeling (Nonclinical information only)

(b) (4)

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/s/

ERIN M RUHLAND
09/08/2023 09:27:18 AM

KIMBERLY P HATFIELD
09/08/2023 01:13:08 PM
I agree with the review and conclusions of Dr. Ruhland.